CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-061/SE2-007

21-062/SE2-008

CORRESPONDENCE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-062/S-008

PRIOR APPROVAL SUPPLEMENT

Bristol-Myers Squibb Company
Attention: Robert E. Kessler, Ph.D.
Director, Regulatory Affairs
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Kessler:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tequin (gatifloxacin) IV, 200 and 400 mg

NDA Number: 21-062

Supplement Number: S-008

Review Priority Classification: Standard (S)

Date of Supplement: January 2, 2001

Date of Receipt: January 3, 2001

This supplement proposes the following change(s):

A change in dosing regimen for the treatment of Acute Exacerbation of Chronic Bronchitis (AECB) to five (5) days duration.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 4, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 3, 2001 and the secondary user fee goal date will be January 3, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the

date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Diana Willard, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/s/

Ellen Frank
1/24/01 05:37:25 PM
NDA 21-062/S-008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-061/S-007

PRIOR APPROVAL SUPPLEMENT

Bristol-Myers Squibb Company
Attention: Robert E. Kessler, Ph.D.
Director, Regulatory Science
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Kessler:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: TEQUIN (gatifloxacin) tablets, 200 mg & 400 mg

NDA Number: 21-061

Supplement Number: S-007

Review Priority Classification: Standard (S)

Date of Supplement: December 21, 2000

Date of Receipt: December 21, 2000

This supplement proposes the following change(s):

A change in dosing regimen for the treatment of Acute Exacerbation of Chronic Bronchitis (AECB) to five (5) days duration

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 9, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 21, 2001 and the secondary user fee goal date will be December 21, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the

date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Diana Willard, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/s/

Ellen Frank
12/28/00 06:01:40 PM
NDA 21-061/S-007

NDA NO. 21-061 REF NO. 007
NDA SUPPL FOR SE8

Bristol-Myers Squibb
Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

December 21, 2000

Renata Albrecht, M.D., Acting Director
Division of Special Pathogens and Immunologic Drug Products
HFD-550
Center for Drug Evaluation and Research
Attention: Document Control Room
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. Albrecht:

Reference is made to NDA No. 21-061, TEQUIN® (gatifloxacin) Tablets, approved December 17,1999. At this time we are submitting a Supplemental New Drug Application (SNDA) in support of the efficacy and safety of 5-day duration of therapy for Acute Exacerbation of Chronic Bronchitis (AECB). This submission is made in accordance with 21 CFR 314.70 and is organized as outlined in the overall Table of Contents in Volume1 of this filing. Additional information can be found in the Reviewer's Guide immediately following this letter.

The efficacy and safety of TEQUIN® in the treatment of AECB is supported by the results of two clinical trials that enrolled a total of 828 patients. An Integrated Summary of Safety and Efficacy (ISS/ISE) is provided in section 3. Proposed revisions to the approved text for labeling is provided in section 2. As agreed in a teleconference held December 6, 2000 and based on Serial No. 206 to IND [redacted], we are also supplying a report provided to us by [redacted] for a 5-day study of AECB that was conducted with no involvement on the part of Bristol-Myers Squibb. This report is not discussed in detail in the ISS/ISE and is being provided for informational purposes only.

As discussed in the December 6, 2000 teleconference, we are also providing a third-party audit of two sites (AI420-064-023 and AI420-064-024) from the AI420-064 study as provided by [redacted] and contained in Section 8/10 of this filing.

SAS Transport files and Case Report Forms are being provided electronically in the SNDA on two CD-ROMs. The combined total size of these files is 760 MB. These electronic components are virus-free as determined by Norton Antivirus Software (Version 5.01.01 for Windows NT) with virus definitions current as of November 30, 2000.

In accordance with the Patient User Fee Section of the Food and Drug Administration Modernization Act of 1997, payment in the amount of $142,870 was sent to the Food and

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Drug Administration, Philadelphia, Pennsylvania on December 18, 2000. This application was assigned the User Fee Identification Number 3997.

Please be advised the Bristol-Myers Squibb considers the information in this application to be confidential and proprietary and therefor we request that no portions thereof be disclosed to third parties under FOI or otherwise without first obtaining written consent from Bristol-Myers Squibb.

If you have any questions regarding this submission, please contact the undersigned at 230-677-6163.

Sincerely,

Robert E. Kessler, PhD.
Director, Regulatory Science

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

N13L

APR 13 2001

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN ("NIDPOE") LETTER

CERTIFIED MAIL – RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Carl Andrew DeAbate, M.D.
Medical Research Centers, Inc.
1020 Gravier Street
New Orleans, Louisiana 70112

Dear Dr. DeAbate:

Between May 30 and June 27, 2000, Food and Drug Administration (FDA) investigators, Ms. Barbara D. Wright and Dr. Mathew T. Thomas, conducted an inspection of the following clinical studies in which you participated:

1. Protocol [ ] titled, "Comparative Safety and Efficacy of [ ] and Cefuroxime Axetil in the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis," and

2. Protocol [ ] titled, "Comparative Safety and Efficacy of [ ] and Clarithromycin in the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis," sponsored by [ ]

The FDA inspection was expanded to review your enrollment of subjects for other clinical studies that included:

3. Protocol [ ] titled, "A Multicenter, Randomized, Double-Blind, Active-Controlled, Comparative Three-Arm Study, Evaluation of the Efficacy and Safety of Oral [ ] 800 mg Once a Day for 5 Days Versus [ ] 800 mg Once a Day for 10 Days Versus Amoxicillin/Clavulanic acid 500/125 mg Three Times a Day for 10 days in the Treatment of Acute Maxillary Sinusitis (AMS) in Adults," and

4. Protocol [ ] titled, "A Multicenter, Randomized, Double-Blind, Comparative Study of Oral [ ] (800 mg Once Daily) Versus Oral Cefuroxime Axetil (500 mg Twice Daily) for Outpatient Treatment of Acute Exacerbation of Chronic Bronchitis in Adults," sponsored by [ ]

5. Protocol[ ] titled, "A Comparative Study of the Efficacy and Safety of Clarithromycin Immediate Release Tablets and Loracarbef Pulvules for the Treatment of Patients with Secondary Bacterial Infection of Acute Bronchitis," sponsored by Abbott Laboratories.

This inspection is part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies are protected.

We note that at the conclusion of the inspection Ms. Wright presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. We have reviewed your letter dated July 20, 2000, in response to the items listed on the Form FDA 483 and find your responses to be unacceptable.

Based on our evaluation of a number of materials including, but not limited to, the establishment inspection report, the documents submitted with that report, information received from sponsors, and your written response dated July 20, 2000, FDA's Center for Drug Evaluation and Research (the "Center") believes that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed) or you repeatedly or deliberately submitted false information.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR 312.70.

A listing of the violations follow. The applicable provisions of the CFR are cited for each violation.

1. You submitted false information to the sponsor, in violation of 21 CFR 312.70(a).

   A. In protocol[ ] you submitted data from sputum samples that did not belong to the subjects identified with the samples. The study sponsor provided FDA with data from its audit of your study site, which revealed that the DNA in sputum specimens did not match the DNA in each subject's blood serum for 35 of the 84 subjects. Furthermore, the results demonstrate that sputum specimens that were purportedly obtained from 26 different subjects actually came from 3 individuals (17 specimens matched profile A, 4 matched profile B, and 5 matched profile C).

B. In protocol [ ] subject [ ] (#66013), whom you reportedly enrolled and followed to completion in the study, did not exist as a unique subject. In your verbal response to the FDA investigator, you stated that subject [ ] was enrolled twice in protocol [ ] under two different names as [ ] (#66003) and [ ] (#66013). Therefore, the data generated for subject [ ] (#66013) is falsely represented. Your response does not adequately explain how this alleged instance of re-enrollment occurred and why it was not detected.

C. In protocol [ ] you reportedly enrolled and followed to study completion a subject identified as [ ] (#3525). We were not able to document that [ ] is a real person.

D. An individual, to whom you entrusted study-related responsibilities, signed an affidavit stating that the data submitted to sponsors regarding subjects' study drug compliance were inaccurate. In the affidavit this individual states that, "...the subject's returned drug was disposed of and 100% drug compliance was recorded. I occasionally disposed of returned drug and recorded 100% compliance myself. I estimate that this occurred no more than 20% of the time."

2. You failed to conduct the study in accordance with the investigational plan, in violation of 21 CFR 312.60.

A. For protocols [ ] and [ ] you failed to collect sputum samples in accordance with the investigational plan. During the FDA inspection, you acknowledged that qualifying sputum specimens were obtained from an unidentifiable number of subjects from outside the clinic because some subjects were unable to produce a sputum specimen on demand. Furthermore, you failed to document the specific instances of sputum collection obtained outside the clinic thereby providing a false impression that all sputum specimens were collected as instructed by the sponsor. In your written response you state that this was not explicitly required by the protocol. However, the sponsor (TAP Pharmaceuticals) informed FDA that, it specifically instructed all clinical investigators during the investigator's meeting that it required the collection of subjects' sputum in the presence of the clinical investigator. Documentation of that meeting indicates that you and your staff were in attendance. Attendees were specifically tested, via an interactive audience response system, on the question of what to do if a patient is unable to produce a sputum specimen at the pre-therapy visit or if the specimen is unacceptable. The unambiguous answer to this question was that if a patient is unable to produce a sputum specimen at the pre-therapy visit or if the specimen is unacceptable the patient is ineligible for the study. This answer was presented to and discussed with the audience immediately after the question.

B. In protocol [ ] you failed to collect sputum samples in accordance with the investigational plan.

3. You failed to personally conduct or supervise the clinical investigation as you committed to do when you signed the investigator statement (Form FDA 1572), in violation of 21 CFR 312.60.

The violations documented above resulted, at least in part, from a serious lack of your direct involvement in the conduct of the study or personal supervision of personnel involved in assisting you with the conduct of those studies. You should recognize that although duties may be delegated, it is the principal investigator who is ultimately responsible for the conduct of a study, and the submission of accurate information to the sponsor and FDA.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, the Center asserts that you have repeatedly or deliberately failed to comply with the cited regulations or repeatedly or deliberately submitted false information to the sponsor or the FDA. The Center proposes that you be disqualified as a clinical investigator. You may reply in writing or at an informal conference in my office to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at (301) 594-0020 to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Stan W. Woollen
Acting Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room #103
Rockville, Maryland 20855

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring all pertinent documents with you, and a representative of your choosing may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with the Center regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and the Center.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. After such a hearing, the Commissioner will determine whether or not you will remain entitled to receive investigational products. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

/S/

Stan W. Woollen
Acting Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
#1 - 21 CFR Part 312
#2 - 21 CFR Part 16
#3 - Agreement